REMARKS/ARGUMENTS

In response to the Office Action of July 26, 2005, Applicants request re-examination and reconsideration of this application for patent pursuant to 35 U.S.C. 132.

Claim Status/Support for Amendments

Claims 1, 39, 40 and 44 have been amended. Claims 2-38 were cancelled in a previous response (filed on December 10, 2004). Claims 39-46 are withdrawn from consideration. It is understood that claims 39-46, drawn to the non-elected invention, will remain pending, albeit withdrawn from prosecution on the merits at this time. If the examined claim of the Group I invention is deemed to be allowable, rejoinder of the remaining claims (39-46) in accordance with the decision in *In re Ochiai* is respectfully requested; since the remaining claims (39-46) are limited to the use of the biopolymer marker of claim 1 (the examined claim of the elected Group I invention).

Claim 1 is under examination. Claims 1 and 39-46 remain pending in the instant application.

No new matter has been added by the amendments to the claims made herein.

Claim 1 has been amended to clearly indicate that the biopolymer marker consisting of SEQ ID NO:4 evidences a link to

Type II diabetes. This amendment is supported by the specification as originally filed; see page 35, lines 14-18, which discloses that an objective of the invention is to evaluate samples containing a plurality of biopolymers for the presence of disease specific biopolymer markers which evidence a link to at least one specific disease state and page 46, lines 6-16, identifies SEQ ID NO:4 as a biopolymer related to the specific disease, Type II diabetes.

Claims 39 and 44 have been amended to remove the term "isolated".

Claim 40 has been amended to provide proper antecedent basis to the term "sample" in parent claim 39.

Request for Rejoining of Claims

Considering that claims 39-46 are limited to the use of SEQ ID NO:4 a search of these claims would encompass this specific sequence. The instant application is related in claim format to several other applications, both pending and issued, of which serial number 09/846,352 is exemplary. In an effort to maintain equivalent scope in all of these applications, Applicants respectfully request that the Examiner consider rejoining claims 39-46 in the instant application, which are currently drawn to non-elected Groups, with claim 1 of the elected Group under the

decision in *In re Ochiai* (MPEP 2116.01), upon the Examiner's determination that claim 1 of the elected invention is allowable and in light of the overlapping search. If the biopolymer marker of SEQ ID NO:4 is found to be novel, methods and kits limited to its use should also be found novel.

Rejection under 35 USC 101

Claim 1, as presented on May 9, 2005, remains rejected under 35 USC 101 because the claimed invention is allegedly not supported by either a specific, substantial, credible or asserted utility or a well-established utility.

First, Applicants note that the Examiner refers to "lane 10 of Figure 4" in the final office action at page 7, last paragraph. However, Figure 4, as originally filed in the instant specification, shows a mass spectral profile and not a gel.

The Examiner asserts that applicant contends that Figure 1 contains samples from normal and Type II diabetes and complement fragments were identified in Band 3 of lane 2 (Type II diabetes). However, the Examiner asserts that when the data is reviewed as a whole it is deemed inconclusive because Band 3 is expressed in all of the lanes (Type II diabetes as well as normal). Therefore, the use of the fragments of Band 3 as markers differentiating between normal and Type II diabetes would require further research to

identify or reasonably confirm their use as substantial because conflicting results are presented in the specification.

Applicants strongly disagree with the Examiner's assertions. First, although the identification of complement fragments was disclosed in the instant specification at page 46, lines 6-16, the band labeled Band #3 in Figure 1 does not contain complement fragments as the Examiner asserts, it contains apolipoprotein A-IV precursor fragments and beta actin fragments and is clearly labeled to contain such fragments. The claimed biopolymer marker (SEQ ID NO:4) was identified as a fragment of the apolipoprotein A-IV precursor protein at page 46, lines 6-16 of the instant specification and thus is recognized to be found in Band 3 as shown in Figure 1.

Although the Examiner asserts that Band #3 is expressed in all of the lanes of the gel shown in Figure 1, a careful observation of the figure reveals that this assertion is incorrect. Band #3 is expressed only in lanes containing samples obtained from Type II diabetes patients (lanes 2-6) and not in lanes containing samples from patients determined to be normal with regard to Type II diabetes (lanes 7-10). Thus, clear differentiation of the claimed biopolymer marker (SEQ ID NO:4) between Type II diabetes patients and normal patients is evident.

In order to illustrate this point, Applicants herein provide

the attached Declaration (and figure) under 37 CFR 1.132. The figure attached to the declaration is entitled "HiQ (scrub) Normal vs. Diabetes Type II" and represents Figure 1 as originally filed. This figure was produced by scanning the original photograph of the gel. No new matter has been added; this figure is simply a clearer copy of Figure 1 as originally filed and is provided to clarify the differential expression of the claimed biopolymer marker (SEQ ID NO:4); i.e to clarify the presence of Band 3 (from which the claimed peptide, SEQ ID NO:4, was isolated) in samples obtained from Type II diabetes patients and the absence of Band 3 in samples obtained from patients determined to be normal with regard to Type II diabetes. The gel shown in the figure does not represent new experimentation; the figure shows a clearer image of the original gel made at the time that the experiments described in the instant specification were first carried out.

Furthermore, Applicants respectfully submit that although all of the lanes have bands in the same comparative areas, the intensity of the bands is not identical, nor does each band necessarily correspond with only one protein.

According to the method of the invention, the criteria for evaluation is the identification of specific ions from the bands in the gel and not the appearance of the band itself; i.e. bands are selected for further analysis based on differential expression

observed in gels but peptides contained within the bands are ultimately identified by mass spectrometry, and not by gel electrophoresis alone. A hypothetical example may serve to clarify. For example, a researcher has found that Band X is differentially expressed between a lung cancer patient and a patient who was determined to be normal with regard to lung cancer. In hope of identifying potential markers for lung cancer, the researcher subjects Band X to mass spectrometry and obtains three distinct mass spectral profiles. Two of these mass spectral profiles match to known proteins, Protein A and Protein B, which the researcher than identifies as potential markers for lung cancer. The fact that multiple peptides were identified from one band does not diminish the value of the peptides as markers since it is the mass spectral profile which is unique and not the band itself. If a peptide is identified in a particular band, then it is present in that band regardless of the presence and/or absence of other peptides/proteins within the same band. Nor is differential expression limited to presence in disease and absence in normal, any differential expression can link a peptide/protein to a disease state (see page 11, lines 9-20 of the instant specification).

The Examiner states that patentability cannot be predicated upon an advantage that has not been expressly or at least

implicitly, disclosed in the application as filed (*Clinical Products v. Brenner* 149 USPQ 475).

The claimed biopolymer marker (SEQ ID NO:4) is shown, in Figure 1 of the instant specification as originally filed, to be differentially expressed in Type II diabetes patients as compared to normal patients. It is acceptable in the art to refer to a differentially expressed peptide as a "marker" and thus link the peptide to the disease condition. For example, Cheng et al. (see attached abstract, Journal of Neural Transmission 103 (4):433-446 1996; reference 1) identify homovanillic acid as a useful marker for early diagnosis of Parkinson's disease since when comparing the levels of homovanillic acid in cerebrospinal fluid, they found a lower level in Parkinson's disease patients as compared with the levels found in age-matched controls.

Accordingly, Applicants expressly show differential expression of the claimed peptide (SEQ ID NO:4) in Type II diabetes versus normal, which, in turn, links the claimed peptide (SEQ ID No:4) to Type II diabetes. Thus, the claimed invention is in harmony with the precedent set by *Clinical Products v. Brenner* since the differential expression (the "advantage") that is disclosed in the application as filed enables the claimed peptide (SEQ ID NO:4) to be patentable as a marker.

Applicants contend that the invention has "real-world" value.

The Examiner asserts that this argument was not found persuasive because utilities that require or constitute carrying out further research to identify or reasonably confirm a "real-world" context of use are not substantial utilities. Apparently, the Examiner believes that Applicants' asserted utility for the instant invention requires further research in order to be deemed "substantial".

If an invention is determined to have "real-world" value, one skilled in the art can use the claimed discovery in a manner that provides some immediate benefit to the public (as established in *Nelson v. Bowler and Crossley* 206 USPQ 881).

The instant invention provides a peptide which was determined to be linked to Type II diabetes, thus, unknown samples can be screened for the presence of the peptide in order to link the sample to Type II diabetes. Since new information about the peptide is provided (a link to Type II diabetes), no additional research is required in order to use the peptide as a diagnostic tool for identification of the claimed biopolymer marker (SEQ ID NO:4) in a sample to link the sample to Type II diabetes.

The incidence of Type II diabetes is increasing in westernized countries as is mortality and morbidity due to its symptoms. Thus, advances in diagnosis and treatment of Type II diabetes are highly desirable and would greatly benefit the

population susceptible to Type II diabetes. The instant invention discloses a peptide (SEQ ID NO:4) which has already been identified as linked to Type II diabetes and thus, represents an advance in diabetes research in its current form; a "real-world" use benefitting the public, which satisfies the precedent set in *Nelson*. Thus, contrary to the Examiner's assertion, the instant invention has "real-world" value.

Furthermore, when considering practical utility ("real-world" utility) relevant evidence is judged as a whole for its persuasiveness in linking observed properties to suggested uses (*Nelson v. Bowler and Crossley* 206 USPQ 881).

The instant specification suggests that the claimed biopolymer marker (SEQ ID NO:4) is useful for diagnostics and/or therapeutics of Type II diabetes since it was found to be differentially expressed in Type II diabetes versus a normal physiological state relative to Type II diabetes. Applicants respectfully assert that the observed differential expression is enough evidence such that one of ordinary skill in the art would be reasonably certain of the practical utility of the claimed biopolymer marker (SEQ ID NO:4).

Situations similar to the situation in the instant case have occurred in the prior art wherein a marker was recognized to have practical utility based upon differences in expression in a

disease state versus expression in a normal physiological state.

For example, Andreasen et al. disclose a study wherein the differences in concentration of β-amyloid (1-42 aa) in cerebrospinal fluid between early- and late-onset Alzheimer's disease was evaluated. Andreasen et al. found that levels of CSF-β-amyloid were decreased in patients with Alzheimer's disease compared with controls and from these findings suggested that CSF-β-amyloid analyses may be of value in the clinical diagnosis of Alzheimer's disease, especially in the early course of the disease, when drug therapy may have the greatest potential of being effective but clinical diagnosis is particularly difficult (see attached abstract of Andreasen et al. Archives of Neurology 56(6):673-680 1999; reference 2).

Since the data of Andreasen et al. was available in the art at the time of the invention, one of skill in the art would be familiar with such practice (suggestion of a differentially expressed peptide for diagnostics) and thus likely to find that linking the observed differential expression of the claimed biopolymer marker (SEQ ID NO:4) to the suggested use of diagnostics and/or therapeutics of Type II diabetes is plausible.

The Examiner states that Applicant contends that the use of SEQ ID NO:4 is well established because a correlation between apolipoprotein A-IV and Type II diabetes is known. However, the

Examiner asserts that the elevation of full length apolipoprotein A-IV does not provide evidence that fragments consisting of SEQ ID NO:4 would also be elevated in Type II diabetes.

Applicants respectfully contend that by requiring a conclusive showing of the elevation of SEQ ID NO:4 in Type II diabetes is requiring the Applicants to meet a standard higher than that which is necessary to satisfy the utility requirement under 35 USC 101, because it has been settled that an applicant is not required to provide evidence sufficient to establish than an asserted utility is true "beyond a reasonable doubt". Instead, evidence will be sufficient if, considered as a whole, it leads a person of ordinary skill in the art to conclude that the asserted utility is more likely than not true (MPEP 2164.07 I C).

Applicants respectfully submit that the article of Verges et al. (reference #4 in the previous response filed on May 9, 2005) was cited as evidence to show that a person of ordinary skill in the art would be exposed to enough knowledge to conclude that the asserted utility for the claimed peptide (SEQ ID NO:4) is more likely than not true. Verges et al. note that increased plasma levels of apoA-IV have been observed in NIDDM (Type II diabetes) patients and want to find out if there is an association between plasma apoA-IV level and the prevalence of macrovascular disease in NIDDM. Verges et al. observe from their experiments that the

levels of apoA-IV are significantly higher in NIDDM patients having macrovascular disease than in NIDDM patients without macrovascular disease. Verges et al. extrapolate from these observations that increased apoA-IV is associated with an increased prevalence of macrovascular disease in NIDDM and suggest that apoA-IV appears to be a marker for macrovascular disease in NIDDM patients.

At page 46, lines 6-16 of the instant specification as originally filed, the claimed peptide (SEQ ID NO:4) is identified as a fragment of apolipoprotein A-IV (apoA-IV) precursor. When one of ordinary skill in the art observes that the claimed peptide (SEQ ID NO:4) is found in Type II diabetes patients and not found in patients determined to be normal with regard to Type II diabetes, they would first want to know whether there is any known connections between apolipoprotein A-IV and Type II diabetes. Thus, one of ordinary skill in the art would be likely to come upon the Verges et al. reference in a search for an answer to this question. After reviewing the teachings of Verges et al., one of ordinary skill in the art would find that increased levels of apolipoprotein A-IV protein has already been reported in Type II diabetes. This data is in agreement with Applicants' findings of increased expression of apolipoprotein fragments in Type II diabetes patients. If a protein has been found at increased levels

in a disease condition, it would not be surprising that fragments of the protein will also be found at increased levels in the disease condition. Accordingly, it is reasonable for one of ordinary skill in the art to believe that the claimed peptide (SEQ ID NO:4), i.e. apolipoprotein A-IV, is more likely than not linked to Type II diabetes.

In conclusion, Applicants respectfully submit that Figure 1 clearly establishes the differential expression of the claimed peptide (SEQ ID NO:4) in Type II diabetes versus a healthy state, thus, a link between the claimed peptide (SEQ ID NO:4) and Type II diabetes is exemplified in the disclosure. This link evidences that the claimed peptide (SEQ ID NO:4) has utility as a marker for Type II diabetes. Based upon all of the above arguments and attached declaration (with figure), Applicants respectfully submit that one of ordinary skill in the art would immediately appreciate why Applicants regard the claimed biopolymer marker (SEQ ID NO:4) as useful.

Accordingly, Applicants assert that the claimed invention has both a specific and a well established utility and respectfully request that this rejection under 35 USC 101 now be withdrawn.

Rejections under 35 USC 112, first paragraph

Claim 1, as presented on May 9, 2005, remains rejected under 35 USC 112, first paragraph since the claimed invention allegedly is not supported by a specific, substantial, credible or a well-established utility, one skilled in the art clearly would not know how to use the claimed invention.

Applicants respectfully disagree with the Examiner's assertions.

It has been established by prior arguments in the instant response (and in previous responses) that the claimed invention has both a specific and a well established utility. Applicants assert that one of skill in the art would know how to use the claimed biopolymer marker (SEQ ID NO:4) as a marker for Type II diabetes; therefore, Applicants respectfully request that this rejection under 35 USC 112, first paragraph now be withdrawn.

Claim 1, as presented on May 9, 2005, remains further rejected under 35 USC 112, first paragraph, as allegedly failing to comply with the enablement requirement. The Examiner asserts that the claim contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains or with which it is most nearly connected, to make and/or use the invention.

The Examiner asserts that Applicant contends that because the disclosure identifies a specific use for sequences consisting of SEQ ID NO:4 the requirement of 35 USC 101 and 35 USC 112, first paragraph should be withdrawn.

Applicants draw the Examiner's attention to page 30 of the response filed on May 9, 2005, wherein it is clear that Applicants assert that the instant invention has both a specific **and a well-established** utility.

The Examiner applies many of the same arguments used to support the rejection of claim 1 under 35 USC 101 to support the instant rejection of claim 1 under 35 USC 112, first paragraph and these arguments have been addressed above in the section entitled "Rejection under 35 USC 101".

Additionally, the Examiner asserts that Applicants' arguments were carefully considered but not found persuasive because the specification must teach how to make and use the invention, not teach how to figure out for oneself how to make and use the invention (*In re Gardner* 166 USPQ 138).

The instant specification discloses that SEQ ID NO:4 was found to be differentially expressed in Type II diabetes patients as compared to patients determined to be normal with regard to Type II diabetes, i.e. SEQ ID NO:4 was found in Type II diabetes patients and not found in normal patients (see Figure 1). This

differential expression of SEQ ID NO:4 enables it to be used as a marker for Type II diabetes, i.e. unknown samples can be tested for the presence of SEQ ID NO:4 in order to determine potential links to Type II diabetes. No further research is required in order for one to use the claimed peptide (SEQ ID NO:4) as a marker for Type II diabetes. Thus, Applicants respectfully submit that the instant specification meets the requirements under 35 USC 112, first paragraph by teaching how to make (identify SEQ ID NO:4 using proteomics techniques) and use the invention (as a marker for Type II diabetes).

The Examiner asserts that Applicant contends that the references of Tascilar et al. and Tockman et al. are not relevant to the instant invention because they do not teach SEQ ID NO:4 and its association to Type II diabetes. The Examiner then asserts that this argument is not found to be persuasive because the references were merely cited to show the state of the art with respect to marker discovery. A rejection is proper though a reference is not prior art when it establishes the level of ordinary skill in the art at the time of the claimed invention (see *Ex parte Erlich* 22 USPQ 2d 1463).

Applicants respectfully submit that the Examiner has incorrectly interpreted Applicants' prior argument regarding the articles of Tascilar et al. and Tockman et al. since nowhere in

the previous response (filed on May 9, 2005) do Applicants state that they believe that either the Tascilar et al. reference or the Tockman et al. reference is not relevant to the instant invention because it does not teach SEQ ID NO:4 and its association to Type II diabetes.

However, Applicants do not disagree that the references show the state of the art with respect to marker discovery. For example, Tockman et al. establishes the level of ordinary skill in the art at the time of the claimed invention. As was discussed in the previous response (filed on May 9, 2005), Applicants assert that Tockman et al. link protein markers to disease in a manner analogous to that of the instant invention.

Tockman et al. state at page 2712s, left column:

"A functional membrane-associated bombesin receptor recently has been isolated from human small cell lung carcinoma (NCI-H345) cells (23), and bombesin-like peptides have been found in the bronchial lavage fluid of asymptomatic cigarette smokers (24). Thus markers of growth factor expression, insofar as they reflect oncogene activation, may also hold promise for the detection of early (preneoplastic) lung cancer."

From this statement, it is clearly evident that Tockman et al. link bombesin with small cell lung cancer and associate it with potential diagnostics for small cell lung cancer based upon

expression. It does not appear that bombesin was "validated" and/or subjected to any "criteria" other than expression prior to this association. Additionally, Tockman et al. state at page 2713s, left column:

"Evidence of a transformed genome, by expression of tumor-associated antigens, oncofetal growth factors, or specific chromosomal deletions has clear biological plausibility as a marker of preclinical lung cancer."

From this statement, it appears that Tockman et al. believe that the expression of certain proteins provides evidence of a transformed genome and since this transformed genome is associated with lung cancer, it is reasonable to believe that these certain proteins are potential markers.

Thus, the teachings of Tockman et al. evidence that one of ordinary skill in the art would be inclined to link protein markers to disease prior to subjecting such markers to the extensive validation which the Examiner appears to believe is a requirement for identification of potential biomarkers.

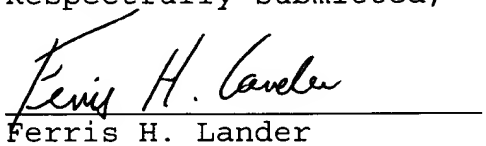
Accordingly, linking of the claimed SEQ ID NO:4 with Type II diabetes would not appear unreasonable to one of ordinary skill in the art since such linking practices were common in the art at least as far back as 1992 (year of publication of Tockman et al.) well before the time of the instant invention.

In conclusion, Applicants claim that the differential expression of SEQ ID NO:4 between Type II diabetes patients and patients determined to be normal with regard to Type II diabetes evidences a link between the claimed peptide (SEQ ID NO:4) and Type II diabetes; a statement which is enabled by the instant specification, as evidenced by the arguments presented herein in both the section under 35 USC 101 and the instant section. Applicants assert that one of ordinary skill in the art when reviewing the instant specification, given the level of knowledge and skill in the art, would recognize the link between the claimed biopolymer marker (SEQ ID NO:4) and Type II diabetes and would further recognize how to use the claimed biopolymer (SEQ ID NO:4) as a marker for Type II diabetes. Thus, Applicants respectfully request that this rejection under 35 USC 112, first paragraph now be withdrawn.

CONCLUSION

In light of the foregoing remarks and amendments to the claims, it is respectfully submitted that the Examiner will now find the claims of the application allowable. Favorable reconsideration of the application is courteously requested.

Respectfully submitted,



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